REMARKS

Applicants respectfully request entry of the amendments hereinabove, reconsideration of the Office Action mailed on April 7, 2004 and allowance of the application.

Applicants also request acknowledgment of the Drawings submitted at the time of filing.

RESPONSE

35 U.S.C. § 112, 2nd Par. Rejection of Claims 3-9, 13-16, 24, 33-38 and 44.

The Examiner rejected Claims 3-9, 13-16, 24, 33-38 and 44 under 35 U.S.C. § 112, 2nd paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. Applicants traverse the rejection of the above-mentioned claims.

(a) Claim 4: In particular, the Examiner rejected Claim 4, citing the phrase "inhibitor has no, or substantially no, activity towards endopeptidase NEP and/or angiotensin converting enzyme" as rendering the claim indefinite, since it is not clear what inhibitors would be encompassed by the Claim.

Applicants respectfully point out that Claim 4 was amended in Applicants' Response, dated December 23, 2003, deleting the phrase "substantially no." Accordingly, the prior amendment renders the objection moot. Applicants note, however, that the prior amendment of Claim 4 was designated as "Previously Amended." Accordingly, Applicants have designated Claim 4 as "Currently Amended," restating the changes therein.

(b) Claim 13: The Examiner rejected Claim 13, contending that the phrase, "NPYi when in use is selective for an NPY associated with male genitalia" renders the claim indefinite, since it is not clear what NPY is associated with male genitalia.

Applicants respectfully point out that Claim 13 was amended in Applicants' Response, dated December 23, 2003, wherein the word "receptor" was inserted for clarification. The phrase as amended reads "NPYi when in use is selective for an NPY receptor associated with male genitalia" (underline denotes amendment). As stated in Applicants' previous response, support for the addition of the word receptor may be found on page 4, lines 23-26. Applicants believe that the amendment submitted on December 23, 2003 renders the objection moot.

(c) Claim 15: The Examiner rejected Claim 15, finding the phrase "NPYi that is capable of selectively increasing the intracavernosal pressure" rendered the claim indefinite as to specifically "what" NPY inhibitors are encompassed by the claims. In particular, the Examiner questions which inhibitors selectively increase the intracavernosal pressure? And, which NPY inhibitors will not selectively increase the intracavernosal pressure?

Applicants amended Claim 15 to clarify that the NPY inhibitors are selective to those NPY receptors associated with the male genitalia. Accordingly, the rejection is now rendered moot.

The Federal Circuit set forth the criteria for the definiteness requirement in SmithKline Beecham Corp. v Apotex Corp., 2004 U.S. App. LEXIS 8107 (Fed. Cir., April 23, 2004).

> The second paragraph of § 112 requires that the specification "conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention." 35 U.S.C. § 112, par. 2 (2000). To satisfy this requirement, the claim, read in light of the specification, must apprise those skilled in the art of the scope of the claim. Miles Labs., Inc. v. Shandon, Inc., 997 F.2d 870, 875 (Fed. Cir. 1993). Moreover, claims need not be "plain on their face in order to avoid condemnation for indefiniteness; rather, what [this court has] asked is that the claims be amenable to construction, however difficult that task may be." Exxon Research & Eng'g Co. v. United States, 265 F.3d 1371, 1375 (Fed. Cir. 2001).

SmithKline, 2004 U.S. App. at 19-20. The Court has cautioned that the breadth of a claim does not render it indefinite. Id. at 22 (citing In re Gardner, 57 C.C.P.A. 1207 (CCPA 1970).

In particular, "a claim is not indefinite merely because its scope is not ascertainable from the face of the claims. . . . [Instead], a claim is indefinite under § 112, par. 2 if it is 'insolubly ambiguous, and no narrowing construction can properly be adopted.'" Amgen Inc. v. Hoechst Marion Roussel, Inc., 314 F.3d 1313, 1342; 65 USPQ.2d 1385 (Fed. Cir. 2003).

In light of the foregoing amendments, Applicants respectfully request reconsideration of the 35 U.S.C. § 112, 2nd paragraph rejections of Claims 3-9, 13-16, 24, 33-38, and 44, since the criteria for definiteness is satisfied. The claims, as amended, particularly point out and distinctly claim the subject matter in which Applicants regard as their invention – the use of selective inhibitors of NPY

associated with male genitalia. These claims, when read in light of the disclosure of the specification, clearly delineates to one of ordinary skill in the art the scope of the claim. As stated in Applicants' previous response, an example of a test to identify NPYi is set forth in the specification at pages 120 and 121. Furthermore, Applicants specifically identify preferred compounds, as well as disclose references containing additional NPY inhibitors.

Accordingly, the claims are unambiguously clear in their scope. Applicants respectfully request reconsideration of the 35 U.S.C. § 112, 2nd paragraph rejections of Claims 3-9, 13-16, 24, 33-38, and 44,

35 U.S.C. § 103(a) Rejection of Claims 3-9, 13-16, 24, 33 and 44.

The Examiner rejected Claims 3-9, 13-16, 24, 33 and 44 as being unpatentable over Hutchison et al (WO98/03492) and Gregor et al. (WO98/07420). The Examiner maintains that Hutchison teaches NYP Y1 specific ligands for treating disorders associated with inappropriate stimulation of of NYP receptors, including *inter alia,* sexual dysfunction. The Examiner states that Gregor teaches the use of compound F50 as a feeding suppressant via its vasodilating properties. The Examiner acknowledges that neither reference expressly teach that NYP inhibitors increase the intracavernosal pressure. Nor do the references teach the claimed dosing of Applicants' invention.

Notwithstanding the above, the Examiner maintains that one of ordinary skill in the art would be motivated by the teachings of Hutchison or Gregor to utilize NPY inhibitors for the treatment of MED by increasing the intracavernosal pressure, since NYP inhibitors are known to be useful as increasing blood flow perfusion. The Examiner states that increasing blood flow to the male genitalia would result in an increase of intracavernosal pressure, thereby causing an erection.

Applicants traverse the rejection of Claims 3-9, 13-16, 24, 33 and 44 and respectfully request that the Examiner reconsider the rejection of the claims. Applicants maintain that the Examiner has not established a *prima facie* case of obviousness.

To establish a prima facie case of obviousness, three basic criteria must be met: (1) There must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; (2) There must be a

reasonable expectation of success; and (3) The prior art reference (or references when combined) must teach or suggest all the claim limitations.

The State of the Prior Art References. As generally described in the reference provided by the Examiner (Harrison's Principles of Internal Medicine, 13th Ed., 1994, pp262-263), in the flaccid state of the penis, arteries within the corpora cavernosa are constricted due to active sympathetic-mediated contraction of smooth muscle in the walls of these structures. Erection begins when relaxation of the smooth muscles lead to dilation of the sinusoids and a decrease in peripheral resistance, causing a rapid increase in arterial blood flow through internal pudendal and cavernosa arteries. Blood is then trapped in the expanding sinusoidal system, which compresses the venules against the tunica albuginea, resulting in venous occlusion. The increase in intracorporeal pressure leads to tumescence and rigidity.

As disclosed in references, the NPY in the penis was believed to have a role in the venous occlusion mechanism, as described above, that sustains an erection. In other words, it was reported that the NPY acts as a vasoconstrictor, causing restriction of penile veins, in particular those which regulate the flow of blood from the penis", (Spec., page 7, lines 8-11), resulting in venous occlusion and, ultimately, an erection. This is supported by the article, Neuromodulation of Penile Erection: An Overview of the Role of Neurotransmitters and Neuropeptides. Argiolas et al. *Progress in Neurobiology,* Vol. 47, pp235-255 (1995), wherein the author states:

> NPY is not involved in the control of the smooth muscles that control penile erection. . . . [R]ecent studies have shown that NPY concentration is very high at the level of the dorsal deep vein and circumflex veins. This localization of NPY together with NA in these major penile veins has led to the suggestion that NPY acts as a neuro-modulator by increasing NA-induced contraction of these blood vessels. . . .[I]t is possible that NPY has a role in the maintenance, if not in the induction of penile erection.

Id. at 241, 1st Col. (citations omitted; emphasis added).

Hutchison et al., also, refers to the vasoconstrictive action of the NPY receptor, leading to *inter alia,* hypertension. (pg 1, lines, 22-23). Hutchison also states that "reports clearly indicate that compounds that inhibit the activity of this protein will reduce hypertension and appetite in animals" (*i.e.* vaso-dilation) (pg 1, lines 24-26). Restated, Hutchison implies that vasodilation would be the result of a NPY inhibitor. Hutchison also states that the physiological disorders may include, *inter alia,* diseases related to sexual dysfunction. Hutchison does not define "sexual dysfunction." Nor does

Hutchison disclose a method of treating MED.

Gregor, on the other hand, discloses agonist and antagonist compounds that are, *inter alia,* feeding stimulants, vasodilating agents and also feeding suppressants, depending upon the manner in which the particular compound interacts with the NPY receptor. Gregor does not specifically identify the compound, F50, as having antagonist properties. Nor does Gregor specifically identify whether F50 has the feeding stimulant property versus feeding suppressant.

The first element of establishing a *prima facie* case, requires some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings.

Given the state of the art at the time of filing, one of ordinary skill in the art would not be motivated to combine the references of Gregor and Hutchison for the treatment or prevention of MED. Hutchison merely discloses that NPY inhibitors may be useful in the treatment of sexual dysfunction, as well as over-eating disorders such as obesity and bulimia. Hutchison does not, however, disclose the treatment of MED. Gregor discloses both agonists and antagonists useful for, *inter alia,* feeding stimulants, vasodilating agents and also feeding suppressants, depending upon the manner in which the particular compound interacts with the NYP receptor. Without experimentation, one would not know whether the F50 compound acts as an inhibitor of NPY (i.e. whether it would have vaso-dilating properties). Given the disclosures of Hutchison and Gregor, one of ordinary skill in the art would not be motivated to combine the references to arrive at Applicants' invention – a method of treating MED.

Even assuming *arguendo* there were motivation to combine the references, which Applicants do not admit, the second and third prongs of the *prima facie* case are not satisfied. Given the state of the art at the time filing, one of ordinary skill in the art would not have a reasonable expectation of success at arriving at Applicants' invention. In particular, one of ordinary skill in the art, would anticipate that an inhibitor of NPY would perform as a vasodilator (Hutchison) of penile veins, in particular those which regulate the flow of blood from the penis. (Spec., page 7, lines 8-11; Argiolas et al.). Since the NPY receptor was believed to have a role in the maintenance of an erection (because of its vaso-constrictive properties), if not the induction, (Argiolas et al.), one of ordinary skill in the art would expect that an inhibitor of NPY would result in flaccidity or detumescence. In other words, one of ordinary skill in the art would expect that an

erection could not be maintained or created, because the penile veins regulating the flow from the penis would be dilated, preventing blood from being trapped in the sinusoidal system. This expectation is supported by the reported high NPY concentration at the level of the dorsal deep vein and circumflex veins, which the NPY is believed to act as neuromodulator by increasing NA-induced contraction of these blood vessels. (Argiolas, p 241).

Furthermore, very small effects of NPY have been reported on cavernosal smooth muscle or penile arteries either in basal conditions or when contracted by NA (noradrenaline), suggesting that NPY is not involved in the control of smooth muscles that control penile erection. (Argiolas, p241). Accordingly, one of ordinary skill in the art would not expect that inhibition of NPY would result in the vaso-dilation of penile veins allowing blood to flow in to the penis. Nor are Applicants aware of any references that expressly teach that neuropeptide inhibitors can increase the intracavernosal pressure. Notwithstanding this expectation, Applicants surprisingly found that administration of a NPY inhibitor results in both an increased blood flow to the penis, as well as restriction of blood flow out of the penis.

In fact, as described above, the art teaches away from Applicants' invention. Accordingly, one of ordinary skill in the art would not reasonably be motivated to use NPY inhibitors for the maintenance or induction of an erection, because the expectation would be that inhibition of the NPY receptor would result in flaccidity or detumescense.

The Examiner states in response to Applicants' arguments filed December 29, 2003, that Applicants do not mention another mechanism that could cause the occlusion of the vein. In short, the increase in intracorporeal pressure, resulting from blood trapped in the expanding sinusoidal system, leads to tumescence and rigidity. Consequently, according to the Examiner, the venous occlusion can be resulted directly from the mechanical compression of the expanding sinusoidal system and not from the activities of NPY.

This is an interesting speculative theory, but the Examiner does not cite any supporting references other than the general summary of the physiology of how an erection is obtained in Harrison's Principles of Internal Medicine. The short paragraph hardly covers the complexities of penile erection and, certainly, does not support the Examiner's statement that venous occlusion is not related to the activity of the NPY receptor. In fact, in the segment of the article provided to Applicants, NPY is not even mentioned. Accordingly, one cannot leap to the conclusion from this article that NPY is

not involved in venous occlusion.

In fact, such a conclusion flies in the face of the prior art – already discussed above, in which the references detail the involvement of NPY, as well as the role of many other neurotransmitters and neuropeptides. The state of the art must be taken as a whole, and when taken as a whole, do not support the Examiner's simplistic position. Even assuming, *arguendo,* that venous occlusion arises from the increase in intracorporeal pressure, resulting from blood trapped in the expanding sinusoidal system, which may lead to tumescence – which Applicants do not admit -- the venal occlusion, resulting from the compression of the venules against the tunica albuginea, may not be sufficient to obtain rigidity and may require secondary activities to provide optimum venal occlusion.

> In particular, "the potentiation of sympathetic tone at the level of penile erection, since a venous occlusion (so-called occlusive venous mechanism, secondary to the compression of penile veins against the undilatable tunica albuginea by the engorgement of corpora cavernosa) is believed by many necessary to prevent the outflow that occurs mainly through these major veins. Therefore, it is possible that NPY has a role in the maintenance, if not in the induction of penile erection."

Argiolas, p241.

Accordingly, given the state of the art as a whole, and the lack of references supporting the Examiner's theory, Applicants maintain that the Examiner's position is unsupported.

Finally, the third prong of the *prima facie* case of obviousness is that the combination of Hutchison and Gregor must teach or suggest all the claim limitations – which they do not do. In particular, Hutchison merely discloses that NPY inhibitors may be useful in the treatment of sexual dysfunction. Hutchison does not define sexual dysfunction and, in particular, does not disclose that the NPY inhibitors are useful for MED. Furthermore, Hutchison does not disclose inhibitors having an affinity for NPY associated with male genitalia. Neither does Hutchison disclose inhibitors having "high" selectivity for NPY associated with male genitalia. Gregor discloses F50, but does not have any disclosure with respect to MED or sexual dysfunction. Accordingly, all of the limitations of Applicants' claims are not taught nor are they suggested.

In summary, the Examiner has not established a *prima facie* case of obviousness. The art when taken as a whole teaches away from Applicants invention. There is no motivation or expectation of success of arriving at Applicants' invention from the combination of the Hutchison and Gregor references, and finally, the references do

not teach all the claim elements. Accordingly, Applicants respectfully request that the Examiner reconsider the rejection of Claims 3-9, 13-16, 24, 33 and 44.

35 U.S.C. § 103(a) Rejection of Claims 34-38.

Claims 34-38 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Hutchison and Viagra monograph, June 1999. In particular, the Examiner contends that one of ordinary skill in the art would be motivated to employ both NPY inhibitor and PDE5 inhibitor together in a method of treating MED, since it was known in the art that both NPY inhibitor and PDE5 inhibitors are useful in treating MED individually. Therefore, according to the Examiner, combining two agents, which are known to be useful to treat MED is *prima facie* obvious.

Applicants traverse the Examiner's rejection of Claims 34-38. Applicants reiterate their points discussed above, regarding the Hutchison reference. In particular, the Hutchison reference does not specifically teach MED. Instead, the reference discloses NPY inhibitors that may be useful in the treatment of sexual dysfunction. The term sexual dysfunction includes both female and male dysfunction. The reference does not, however, disclose inhibitors specifically useful for MED. Accordingly, it was not known in the art that NPY inhibitors were useful in treating MED.

At best, it may have been obvious to try the combination (which Applicants deny), but obvious to try is not the test for obviousness. American Hosp. Supply Corp. v. Travenol Lab., Inc., 223 USPQ 577, 582 (Fed. Cir. 1984). In any event, given the state of the art at the time of the invention, one of ordinary skill in the art would not have a reasonable expectation that NPY inhibitors would be useful in the treatment of MED, since one would have expected that an NPY inhibitor would result in detumescense.

Even if the combination were obvious – which Applicants do not admit – one of ordinary skill in the art would not expect the marked enhancement of the ICP. Applicants demonstrated that the potentiation of ICP induced by PDE5 inhibition can be further potentiated by co-administration of a NPY inhibitor. (Spec. Fig. 10 and text, pp. 125-126).

Accordingly, the combination of Hutchison and Viagra monograph do not render Claims 34-38 obvious.

CONCLUSION

If the Examiner feels that any issues remain unresolved, please telephone the undersigned at 860-715-4288 to expedite resolution of such issues.

In view of the foregoing comments and amendments, no issues are seen to remain. This case is accordingly believed to be in condition for allowance, and a Notice of Allowance is courteously solicited.

Respectfully submitted,

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